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(54) Title: CELLULOSIC PARTICLES SUITABLE FOR CHIRAL SEPARATION

(57) Abstract: In a method of producing spherical derivatized cellulosic particles suitable for chiral separation a solution of amorphous cellulose having free hydroxy groups is first prepared from crystalline cellulose in a first step and spherical porous matrix particles are then manufactured from the solution of amorphous cellulose under high shear stress conditions in a second step. The hydroxy groups are derivatized before or after the second step.

CELLULOSIC PARTICLES SUITABLE FOR CHIRAL SEPARATION

The present invention refers to a method of producing cellulosic particles suitable for chiral separation as well as the use of such particles.

A large number of biologically active substances, such as drugs, herbicides, pheromones, and insecticides, exist as two optical isomers of different specificity (enantiomers). These chiral molecules do not have a plane of symmetry and are therefore not superposable on their mirror image. The synthesis of these compounds by means of conventional methods results in a racemic mixture, i.e. substantially equal amounts of both enantiomers.

However, the enantiomers of a drug normally have different therapeutical effects since they exhibit differences in pharmocokinetics, pharmacodynamics as well as toxicology. Frequently, only one of the enantiomers in a racemic mixture exhibits the desired biological activity. The other enantiomer may lack this activity or may even cause severe side-effects. A well-known example is the administration of Neurosedyne, whereby one of the enantiomers of the drug was responsible for the surprising side-effects at that time. Thus, in order to achieve an optimal therapeutic effect with a minimum of undesired side-effects only one of the enantiomers should be administrated.

Consequently, authorities now demand that prior to registration both enantiomers of a new drug must be tested individually with reference to their pharmaceutical activity.

Also, from environmental point of view it is of great importance that herbicides as well as other kinds of biocides have an optimal enantiomer composition and that there exist analytical methods for following the transportation and biodegradation of these substances at different levels of an ecological system.

In order to separate an enantiomer from a mixture with optical resolution several methods have been attempted, recrystallization of diasteromeric salts, membrane separation and enzymatic degradation. However, these methods are limited to a few specific compounds.

Lately, a separation of enantiomers can be accomplished with chromatographic methods by using chiral stationary phases. However, many different kind of chiral stationary phases are employed, which primarily is due to the relative narrow application window of each of these phases. Furthermore, the majority of the phases are expensive to use in a preparative scale.

A chiral stationary phase is normally prepared by immobilization a chiral selector, for instance a pure enantiomer, to a supporting particle. The particles are packed in a column of glass or steel, which is connected to chromatographic equipment. The most frequently used selectors are different kinds of proteins and derivatized carbohydrates.

Such a carbohydrate is crystalline cellulose. The morphology of cellulose has been found to be of great importance in the chiral separation mechanisms (Hesse and Hagel, Chromatographia 9:62, 1976). This has resulted in the development of microcrystalline triacetylcellulose (Isaksson *et al.*, J. Chromatogr. 498:257, 1990) as well as crystalline triacetylcellulose II (Shibata *et al.*, J. Liq. Chromatogr. 9:313, 1986) chiral stationary phases in chromatography.

In this connection the term crystalline cellulose comprises any crystalline form of cellulose including liquid crystalline cellulose as well as native fibrous cellulose. Microcrystalline cellulose triacatete, prepared by heterogenous acetylation of native cellulose, has a crystalline structure different from triacatete recovered from solution (Okamoto *et al.*, Chemistry Letters (1984)

pp 739-744). These unlike crystal structures of the triacetates seem responsible for the reversed elution order of Troegers base. (Chanzy and Roche, J. Pol. Sci. Polym. Phys. Ed. 12:1117, 1974; *ibid* 13:1859, 1975). Thus, the crystallinty of the cellulosic material has up to now been a prerequisite of a successful enantiomer separation.

Irregular particles of pure micro crystalline cellulose with derivatives thereon have been used as a chiral stationary phase in the separation enantiomers. In US 4,818,394 a useful chiral phase is shown, which comprises a crystalline cellulose derivative adsorbed or immobilized to a silica particle. The particles are obtained by adding a solution of a cellulose derivative to a suspension of silica particles with large pores. After evaporation and rinsing the particles are used as chiral stationary phases. However, columns containing these silica particles are expensive and the particles of large pore-sizes have a relatively short useful life.

In US 5,656,158 spherical particles (beads) of derivatized and regenerated crystalline cellulose have been prepared. Difficulties concerning the preparation of the derivatized particles are discussed, but no chromatographic use of any chiral phase is reported.

The purpose of the invention is to achieve a method of producing spherical cellulosic particles, whereby the above-mentioned problems are eliminated, which method makes possible to prepare derivatized macroporous microbeads for chromatographic separations of specific compounds and specifically for the separation of chiral compounds.

Another purpose of the invention is to achieve a method of producing spherical cellulosic particles, whereby the purity of starting materials, products, and different kinds of pharmaceutical preparations can be determined. Furthermore, the inventive method results in that enantiomers in biological fluids can be effectively and

quantitatively analyzed. It is also possible to more thoroughly characterize the biological effects of enantiomers in biological systems and to accomplish preparative chromatographic baseline separations of enantiomers of both enantiomers for biological tests. Enantiomeric metabolities can be isolated from complicated biological matrices, such as urine and tissue.

In order to achieve these purposes, the method according to the invention has been given the characterizing features of claim 1.

The inventive method concerns the production of derivatized spherical cellulosic particles suitable for chiral separation, the steps of which comprises the preparation from crystalline cellulose of a solution of amorphous cellulose having free hydroxy groups, and then manufacturing spherical porous matrix particles of amorphous cellulose from this solution under high shear stress conditions. The hydroxy groups can be derivatized before or after the manufacturing of the particles by means of conventional techniques.

The invention also concerns the use of porous matrix particles of derivatized amorphous cellulose as a separating agent for a chemical substance. Suitable particles are spherical particles produced according to the inventive method.

In this connection matrix particles are rigid porous spheres having a randomn pore network. The physical structure of matrix particles can range from dense to highly porous. The molecular and macroscopic properties of the particles can be tailored to exclude specific geometric and morphological structures and to encompass specific functional requirements.

The solution of amorphous cellulose is prepared by dissolving the crystalline cellulose in a reactive solvent. In this connection the term crystalline cellulose includes

crystalline and fibrous cellulose, and the term reactive solvent refers to any solvent having the capacity of transforming crystalline cellulose to amorphous cellulose.

Examples of suitable reactive solvents are copper ammonium hydroxide, quaternary ammonium hydroxide, a transition metal complex, and litium chloride in dimethylacetamide. Preferably, the reactive solvent is lithium chloride in N,N-dimethylacetamide (DEMAC). In this case the concentration of lithium chloride is up to 15 weight%.

It is also preferred that swelling the crystalline cellulose in a hydrophilic solvent precedes the dissolution of the crystalline cellulose. The hydrophilic solvent can be water, methanol, or a mixture thereof. The hydrophilic solvent is subsequently removed from the swelled cellulose.

Spherical particles are then manufactured from the regenerated amorphous cellulose by means of any suitable technique for the preparation of beads, preferably with an internal pore structure. It is appropriate to manufacture porous particles by forming individual spherical droplets of the solution of amorphous cellulose by means of a mechanical disintegration.

Amorphous cellulose, prepared as described above, is allowed to expiate upon a rotating disc, on which the solution of amorphous cellulose is exposed to high shear stress conditions. These conditions ensure that no reversion to crystalline cellulose will take place during the manufacturing of porous matrix particles.

The shear stress effecting exponent m can be determined according to the equation $= * ^{m}$ as described in Wikström et al. (J. Food Science, vol 59(5), 1994, pp.1077-1080). At 4 200 rpm and a temperature of 33 °C a cellulose solution according to the invention exhibits a m value of 0.97. Consequently, this cellulose solution behaves as a Newtonian fluid and does thus not contain any crystalline

material. It retains its structure of low order during the expiation and drop formation.

Spherical droplets are captured in a hydrophilic solvent, from which they are harvested. The hydrophilic solvent can be water and/or methanol, and is preferably water.

Preferably, mechanical disintegration is performed by means of centrifugal action from a rotating disk. Suitable spinning disk techniques are shown in US 4,978069 and in the Swedish patent application No 9904345-7. In this way amorphous, porous, and spherical particles in the range from 20 to 200 µm can be produced. Comparative measurements by means of NMR of fibrous microcrystalline cellulose as well as cellulose particles produced according to the invention reveals that the inventive spherical porous matrix particles consists of completely disordered celllose only.

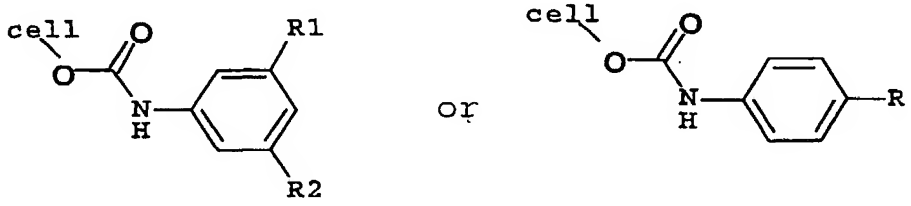
By assuring that thoroughly homogenous porous particles without any crystallinity in the cellulose matrix a more efficient enantiomer separation can be obtained. Large quantities of non-crystalline cellulose particles with a very narrow size distribution can be prepared at low costs. Almost mono disperse particles are obtained which possess excellent chromatographic performance.

The free hydroxy groups of the amorphous cellulose can be subsequently derivatized by suspending the porous particles in a hydrophobic solvent and adding a derivitizing agent. Of course, the derivitizing can be accomplished prior to the manufacturing of the porous particles. However, a derivatization of the particles is preferred since simple and straightforward synthetic methods can be used without the chromatographic performance being impaired.

Suitable hydrophobic solvents are hexane, heptane , octane, toluene, benzene, xylene, nitro-benzene, chloro-

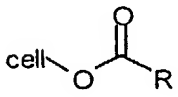
benzene, quinoline, and pyridine. Preferably, hexane, heptane , octane, toluene, or xylene is used.

The hydroxy groups of cellulose are in the derivatization of the particles converted to ethers, esters, or carbamates by synthetic procedures well-known within the art. Preferably, the hydroxy groups of cellulose are derivatized by means of etherificationm to a cellulose phenylcarbamate. Such a cellulose phenylcarbamate has the structure:

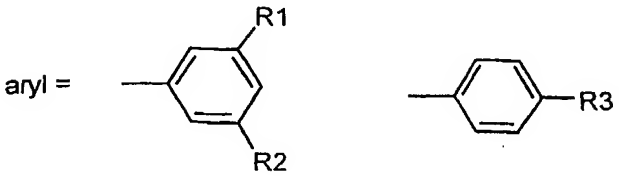


In these structures R, R_1 and R_2 are independently hydrogen, halide, alkyl, alkenyl, alkynyl, aryl, haloalkyl, nitro, formyl, acyl, hydroxyalkyl, alkoxy, hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl, carboxy, carboxyalkyl, carboxyamide, carboxyamidealkyl, amino, aminoalkyl, or isocyanate. Alternatively, the free hydroxy groups of the amorphous cellulose are derivatized by means of esterification to a cellulose ester. The structure obtained is given below with the aryl group further explained.

Cellulose ester



R = alkyl or aryl



In the aryl groups R1, R2, and R3 are independently hydrogen, halide, alkyl, alkenyl, alkynyl, aryl, haloalkyl, nitro, formyl, acyl, hydroxyalkyl, alkoxy, hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl, carboxy, carboxyalkyl, carboxyamide, carboxyamidealkyl, amino, aminoalkyl, or other.

It is preferred to form a three dimensional cross-linked structure within porous particles of amorphous cellulose in order to improve the performance in chiral separation. The cross-linking of the porous particles can take place by adding a cross-linking agent to the hydrophobic solvent before or after the derivatisation of the hydroxy groups of the amorphous cellulose. Preferably, the hydrophobic solvent then contains at least one hydrophilic additive.

The cross-linking agent can be an alkylphenyl-diisocyanate, a dialdehyde, an aliphatic diacid, or an aromatic diacid. The cross-linking of said porous particles is preferably performed within a degree from 5 % to 10 %.

Particles of amorphous cellulose produced according to the inventive method can be used as a separating agent for a chemical substance. The porous particles are especially adapted to be used as an isomer separating agent in chromatography, especially in various fields of life sciences, in which there is a great need of accurate, fast and cheap procedures of separation of structurally related substances as enantiomers. The particles are also suitable for preparative separations of enantiomers of drug substances and other large scale applications.

A special advantage of particles produced according to the invention is that the chromatography can be performed with a hydrophobic mobile phase. Suitable hydrophobic eluents are alkanes, alcohols, amines, or mixtures thereof. Mixtures of such hydrophobic mobile phases can be

produced, which improve the racemic resolution of the chemical substance.

EXAMPLES

Example 1. Preparation of chiral stationary phases.

Solubilized cellulose was prepared suspending fibrous cellulose in water, and the suspension was allowed to stand overnight. Then the cellulose was successively rinsed for 1 h with water, methanol, and DEMAC, and finally allowed to dry under suction on the same glass filter which was used for the washing procedures.

The so rinsed and dried cellulose material was dissolved in DEMAC containing less than 10 wt% lithium chloride, whereby a homogenous solution can be obtained to a concentration up to 10%.

Particles were then produced by dropping the cellulose solution in water and/or methanol. This exposure exchanges the DEMAC of the particles with water or methanol, whereby the cellulose drops will gel and generate spherical amorphous porous matrix particles. By utilizing the above-mentioned spinning disk technique for the mechanical disintegration of the cellulose solution spherical particles in the range from 20-500 microns can be produced.

By these procedures large quantities of particles can be preparad, which have a very narrow particle size distribution of almost monodispersive particles and exhibit excellent chromatographic performance.

Example 2. Heterogen phase synthesis.

The particles produced as above are in heterogen phase synthesis reacted with anhydrides or aromatic isocyanates using an organic medium to give the corresponding esters or carbamates. These methods are classical and well known within the art.

After washing and eventual exchange of solvent the beads can be used in chromatography.

Example 3. Chromatography.

A column of particles produced according to the invention was prepared and packed by using a conventional slurry technique. The column (200 x 10 mm; length x inner diameter) was first eluted with several column volumes of isopropanol and then with the mobile phase to be used in order to obtain chiral separation of optical isomers of different specificity. Enantiomeric separation was performed on an acidic (naproxen) as well as a basic drug (propanolol).

A standard chromatographic equipment with UV detection was used. The mobile phase comprised of a mixture of n-hexane and isopropanol. The samples were introduced to the column by means of a Reodyne injector equipped with a 200 µl loop. The eluent was monitored at 280 nM at a flow rate of 1-3 ml/min. The resolution (Rs) of the separation was calculated according to standard methods.

Enatiomeric separation of naproxen

Mobile phase: n-hexane/isopropanol (99/1; vol/vol)

Flow rate: 2 ml/min

UV: 280 nm

Rs: 1.5 (base line separation)

Enantiomeric separation of propranolol (a β-blocker)

Mobile phase: n-hexane/isopropanol (99/1; vol/vol)

Flow rate: 2 ml/min

UV: 280 nm

Rs: 1.5 (base line separation)

Example 4. Pre-manufacturing synthesis.

A batch of porous spherical particles was produced according to the invention by means of dissolving micro-crystalline cellulose after the fibrous (crystalline) cellulose had been completed substituted with phenyl-carbamate. The so derivatized cellulose was first dissolved in DEMAC to 2-6% and is then disintegrated into spherical particles by using the same rotating disc technique as described above. The particles were catched in water.

After sieving and removal of excess water the particles were sequentially subjected to a solvent change *via* methanol to hexan/iso propyl alcohol as described above. The particle mean size was 35 µm.

A column (5 mm in diameter and 200 mm long) was packed with a 50% gel slurry and the gel bed settles under a flow of 0.5 ml/min. Enantopmeric separations were performed as above (paper speed = 0.1 mm/min; A = 0.025; sample volume = 25 µl) and the results obtained resemble closely those from separations obtained with *post*-manufacturing substitution.

CLAIMS

1. A method of producing derivatized cellulosic particles suitable for chiral separation, c h a r a c - t e r i z e d in that a solution of amorphous cellulose having free hydroxy groups is first prepared from crystalline cellulose in a first step and spherical porous matrix particles are then manufactured from said solution of amorphous cellulose under high shear stress conditions in a second step, said hydroxy groups being derivatized before or after said second step.

2. The method as in claim 1, c h a r a c t e r - i z e d in that it further comprises cross-linking said spherical porous particles before or after said derivatization of said hydroxy groups.

3. The method as in claim 1, c h a r a c t e r - i z e d in that said solution of amorphous cellulose is prepared by dissolving said crystalline cellulose in a reactive solvent.

4. The method as in claim 3, c h a r a c t e r - i z e d in that said reactive solvent is copper ammonium hydroxide, quaternary ammonium hydroxide, a transition metal complex, or litium chloride in dimethylacetamide.

5. The method as in claim 4, c h a r a c t e r - i z e d in that said reactive solvent is litium chloride in dimethylacetamide.

6. The method as in claim 5, c h a r a c t e r - i z e d in that said litium chloride in dimethylacetamide has a concentration of up to 15 weight%.

7. The method as in claim 3, c h a r a c t e r - i z e d in that said dissolution of said crystalline cellulose is preceded by swelling said crystalline cellulose in a hydrophilic solvent and removing said hydrophilic solvent from said swelled cellulose.

8. The method as in any of claims 1-7, c h a r - a c t e r i z e d in that said spherical porous particles

are manufactured by forming individual spherical droplets of said solution of amorphous cellulose by means of mechanical disintegration of the same under high shear stress conditions, said spherical droplets being captured in a hydrophilic solvent.

9. The method as in claim 7 or 8, characterized in that said hydrophilic solvent is water and/or methanol.

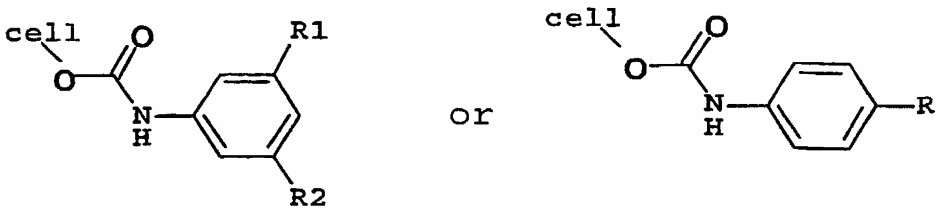
10. The method as in claim 9, characterized in that said mechanical disintegration is performed by means of centrifugal action from a spinning disk.

11. The method as in claim 1, characterized in that said hydroxy groups of said amorphous cellulose are derivatized in a hydrophobic solvent by adding a derivitizing agent to the same.

12. The method as in claim 11, characterized in that said hydroxy groups of cellulose are by means of synthetic procedures converted to ethers, esters, or carbamates.

13. The method as in claim 12, characterized in that said hydroxy groups are derivatized by means of etherification to a cellulose phenylcarbamate.

14. The method as in claim 13 characterized in that said cellulose phenylcarbamate has the structure

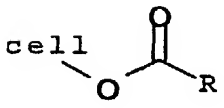


wherein R, R_1 and R_2 are independently hydrogen, halide, alkyl, alkenyl, alkynyl, aryl, haloalkyl, nitro, formyl, acyl, hydroxyalkyl, alkoxy, hydroxyalkoxy, hydroxyalkenyl,

hydroxyalkynyl, carboxy, carboxyalkyl, carboxyamide, carboxyamidealkyl, amino, aminoalkyl, or isocyanate.

15. The method as in claim 12, characterized in that said hydroxy groups are derivatized by means of esterification to a cellulose ester.

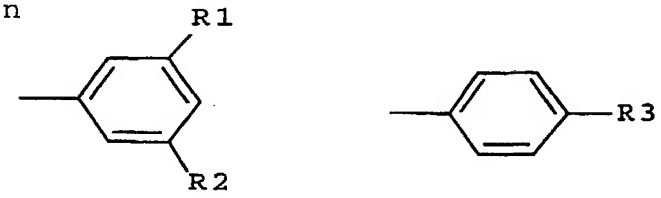
16. The method as in claim 15 characterized in that said cellulose ester has the structure



R = alkyl or aryl,

wherein

aryl =



wherein R1, R2, and R3 are independently hydrogen, halide, alkyl, alkenyl, alkynyl, aryl, haloalkyl, nitro, formyl, acyl, hydroxyalkyl, alkoxy, hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl, carboxy, carboxyalkyl, carboxyamide, carboxyamidealkyl, amino, aminoalkyl, or other.

17. The method as in claim 2 and 11, characterized in that said cross-linking of said spherical porous particles is performed by suspending the same in a hydrophobic solvent and by adding a cross-linking agent to the same.

18. The method as in claim 17, characterized in that said cross-linking agent is an alkyl-phenyldiisocyanate, a dialdehyde, an aliphatic diacid, or an aromatic diacid.

19. The method as in claim 17 or 18, c h a r a c - t e r i z e d in that said cross-linking of said spherical porous particles is performed from 5 % to 10 %.

20. The method as in any of claim 11-19, c h a r - a c t e r i z e d in that said hydrophobic solvent is a aromatic or aliphatic solvent which contains at least one hydrophilic additive.

21. Cellulosic particles produced according to any of claims 1-20.

22. Use of porous matrix particles of derivatized amorphous cellulose as a separating agent for a chemical substance.

23. Use as in claim 22, c h a r a c t e r i z e d in that said particles of derivatized amorphous cellulose are used as an isomer separating agent in chromatography.

24. Use as in claim 23, c h a r a c t e r i z e d in that said chromatography is performed with a hydrophobic eluent as a mobile phase.

25. Use as in claim 24, c h a r a c t e r i z e d in that said hydrophobic mobile eluent is an alkane, an alcohol, or an amine, or a mixture thereof.

26. Use as in claim 25, c h a r a c t e r i z e d in that said mixture of said hydrophobic eluents is used in order to improve the racemic resolution of said chemical substance.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01310

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C08B 15/00, B01J 2/02, B01J 20/30, G01N 30/48 // C08J 3/14, C08J 9/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C08B, B01J, G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN & jp 08-283457 A (CHISSO CORP), 29 October 1996 (1996-10-29) abstract	22
A		1-21,23-26
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A	US 5066793 A (ERIC FRANCOTTE ET AL), 19 November 1991 (19.11.91), column 1, line 56 - line 68; column 4, line 52 - line 65, abstract	1-26
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 2002	14 -11- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Monika Bohlin/Els Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01310

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0527236 A1 (DAICEL CHEMICAL INDUSTRIES, LTD.), 17 February 1993 (17.02.93), page 2, line 19 - line 38; page 3, line 23 - line 29, abstract, claims	1-26
A	EP 0121776 A1 (DAICEL CHEMICAL INDUSTRIES CO., LTD.), 17 October 1984 (17.10.84), page 2, line 31 - page 3, line 13, abstract	1-26
A	US 5656158 A (JOHN W. RUSSELL), 12 August 1997 (12.08.97), column 1, line 29 - line 61, abstract	1-26
A	EP 0706982 A1 (DAICEL CHEMICAL INDUSTRIES, LTD.), 17 April 1996 (17.04.96), page 2, line 11 - line 31; page 4, line 20 - line 32, abstract	1-26
A	US 5889180 A (BETH MC CULLOCH ET AL), 30 March 1999 (30.03.99), column 1, line 7 - line 28; column 4, line 47 - line 50, abstract	1-26
A	GB 2152936 A (DAICEL CHEMICAL INDUSTRIES LIMITED), 14 August 1985 (14.08.85), page 1, line 57 - line 61, abstract, claims	1-26
A	US 4663447 A (KAZUHIRO YAMAZAKI ET AL), 5 May 1987 (05.05.87), column 2, line 10 - line 19, abstract, claims	1-26
A	US 4683341 A (KUNIO ISHII ET AL), 28 July 1987 (28.07.87), column 3, line 44 - column 4, line 7, abstract, claims	1-26

INTERNATIONAL SEARCH REPORT

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PCT/SE 02/01310

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5026841 A (ERIC FRANCOTTE ET AL), 25 June 1991 (25.06.91), column 1, line 67 - column 2, line 5, abstract, claims	1-26
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A	WO 9931141 A2 (THüRINGISCHES INSTITUT FüR- UND KUNSTSTOFF-FORSCHUNG E.V.), 24 June 1999 (24.06.99), abstract, claims	1-26
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